32. A method for identifying a candidate compound useful for modulating meiosis in a cell, comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) determining the expression of the MSH5 gene or the activity of MSH5 in the presence and absence of said test compound;

c) selecting a compound that modulates the expression of the MSH5 gene or the activity of MSH5; and

d) identifying said compound as being a candidate compound useful for modulating meiosis in a cell.

REMARKS

Claims 13, 14, and 22-29 were pending in the present application. Claim 22 has been cancelled, without prejudice, claims 13, 23 and 29 have been amended, and new claims 30-32 have been added. Accordingly, after the amendments presented herein have been entered, claims 13, 14, and 23-32 will remain pending. For the Examiner's convenience, the currently pending claims are set forth herein in Appendix A.

Applicants submit herewith a "Version with Markings to Show Changes Made," which indicates the specific amendments made to the claims.

Support for the new claims and the claim amendments presented herein can be found throughout the specification, including the originally filed claims. Specifically, support for the amendments to claim 13 and for new claim 30 may be found, for example, in originally filed claim 22 and at page 14, line 30 through page 15, line 13 of the specification. Support for new claims 31 and 32 may be found at, for example, page 14, line 30 through page 15, line 13 and at page 19, line 33 through page 20, line 35 of the specification.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Election/Restrictions

Applicants gratefully acknowledge the Examiner's indication that "[u]pon review of the claims and reasons for traverse, the restriction requirement has been withdrawn" and that "[c]laims 13 -14 and 22 -29 are pending and have been considered on the merits."

Rejection of Claims 13-14 and 22-29 Under 35 U.S. C. §112, Second Paragraph

The Examiner has rejected claims 13-14 and 22-29 under 35 U.S. C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that

> [c]laims 13 -14 and 22 -29 are drawn to a method for identifying a compound, however are rendered vague and indefinite because the claim appears to omit essential steps in the method. It is unclear how one would identify a compound which modulates by simply determining the effect of the compound. Moreover, it is unclear what effects, observations or demonstrations must occur to thereby identify the compounds which do or do not modulate MSH5 activity. As stated, it would appear that any test compound would modulate MSH5 activity. For example, after contacting a test compound with MSHS and determining the effect, the compound has been identified as one which modulates the activity, regardless of whether the compound inhibits, stimulates or has no effect on MSH5 activity.

With respect to claim 23, the Examiner is of the opinion that this claim "is rendered vague and indefinite for reciting 'capable of' because the phrase fails to define if the recited functional effect actually occurs or not."

With respect to claim 29, the Examiner is of the opinion that this claim "is rendered indefinite for reciting 'has an effect' because it is unclear what the effect must be. For example, is the substrate is inhibited, stimulated, destroyed, deactivated?"

Applicants respectfully traverse the foregoing rejection on the grounds that claims 13-14 and 22-29 are clear and definite. However, in the interest of expediting prosecution, Applicants have amended claims 13, 23 and 29, thereby rendering the foregoing rejections moot.

The amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 13 and 23 under 35 U.S.C. §102(e)

The Examiner has rejected claims 13 and 23 under 35 U.S.C. §102(e) as being anticipated by Fishel *et al.* (U.S. Patent No. 6,333,153). In particular, the Examiner is of the opinion that

> Applicant claims a method for identifying a compound which modulates MSHS activity, the method comprising a) contacting MSH5 with a test compound, and b) determining the effect of the test compound on the activity ofMSH5, wherein the compound is capable of modulating MSH5 expression. Fishel teaches a method for determining if a composition affects (or modulates) expression of a gene encoding a MutS homolog (MSH) (col.9, lines 10-15) wherein the MutS homolog may be MSH5 (col. 4, line 35-40). The method comprises administering the test composition (or compound) to a cell containing the MutS homolog (or MSH5) and a cell which does not contain the MutS homolog followed by observing phenotypic effects on the cells to determine if the compound affects (or modulates) MutS homolog activity (col. 9, lines 29-45).

Applicants respectfully traverse the foregoing rejection on the grounds that the pending claims are not anticipated by Fishel *et al.*

For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 13, and claims depending therefrom, are directed to methods for identifying a candidate compound useful as a contraceptive by contacting MSH5 with a test compound;

determining the activity of MSH5 in the presence and absence of the test compound; selecting a compound that modulates the activity of MSH5; and identifying the compound as being a candidate compound useful as a contraceptive.

Claim 30, and claims depending therefrom, are directed to methods for identifying a candidate compound useful as a contraceptive by contacting a cell expressing MSH5 with a test compound; determining the expression of the MSH5 gene or the activity of MSH5 in the presence and absence of the test compound; selecting a compound that modulates the expression of the MSH5 gene or the activity of MSH5; and identifying the compound as being a candidate compound useful as a contraceptive.

Claim 31, and claims depending therefrom, are directed to methods for identifying a candidate compound useful for modulating meiosis in a cell by contacting MSH5 with a test compound; determining the activity of MSH5 in the presence and absence of the test compound; selecting a compound that modulates the activity of MSH5; and identifying the compound as being a candidate compound useful for modulating meiosis in a cell.

Claim 32, and claims depending therefrom, are directed to methods for identifying a candidate compound useful for modulating meiosis in a cell by contacting a cell expressing MSH5 with a test compound; determining the expression of the MSH5 gene or the activity of MSH5 in the presence and absence of the test compound; selecting a compound that modulates the expression of the MSH5 gene or the activity of MSH5; and identifying the compound as being a candidate compound useful for modulating meiosis in a cell.

The sections of Fishel *et al.* that the Examiner relies upon for the instant rejection (see *supra*) indicate that Fishel *et al.* teach methods for

> determining whether a composition affects expression of a gene selected from the group consisting of the p53 gene and a gene encoding a MutS homolog. This method comprises administering the composition to ***a first cell derived from a non-human mammal which is nullizygous for one of the p53 gene and the gene encoding a MutS homolog***. A phenotype of the first cell is compared with the phenotype of a second cell derived from a non-human mammal of the same type

> which is not nullizygous for the one of the p53 gene and the gene encoding a MutS homolog, ***wherein the phenotype is selected from the group consisting of inappropriate fetal apoptosis and a predisposition for carcinogenesis***. A difference between the phenotype of the first cell and the phenotype of the second cell is an indication that the composition affects expression of the other of the p53 gene and the gene encoding a MutS homolog. (***Emphasis added***).

Fishel *et al.* do not teach or suggest any association between MutS homologs, such as MSH5, and contraception or meiosis. Neither do Fishel *et al.* teach or suggest methods for identifying candidate compounds useful as contraceptives or useful for modulating meiosis.

Since Fishel *et al.* fail to teach each and every element of the pending claims this reference does not anticipate the claims. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this section 102(e) rejection.

Rejection of Claims 13-14 and 23-29 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 13-14 and 23-29 under 35 U.S.C. §103(a) as being unpatentable over Fishel *et al.* (U.S. Patent No. 6,333,153) in view of Tartaglia *et al.* (U.S. Patent No. 5,972,621). In particular, the Examiner is of the opinion that

> Applicant claims a method for identifying a compound which modulates MSH5 activity, the method comprising a) contacting MSH5 with a test compound, and b) determining the effect of the test compound on the activity of MSH5. Specifically, the compound inhibits MSH5 activity, is capable of modulating MSH5 expression, is an antisense MSH5 nucleic acid, small molecule, MSH5 antibody, peptide, peptidomimetic, or has an effect on an MSH5 substrate. Fishel teaches a method for determining if a composition affects (or modulates) expression of a gene encoding a MutS homolog (MSH) (001.9 line 10-15) wherein the MutS homolog m,ay be MSH5 (col.4 line 35-40). The method comprises administering the test composition (or compound) to a cell containing the MutS homolog (or MSH5) and a cell which does not contain the MutS homolog followed by observing phenotypic effects on the cells to determine if the compound effects (or modulates) MutS homolog activity (col.9line 29-45). Fishel does not teach the method wherein the test compound inhibits MSH5 activity, is an antisense nucleic acid molecule, small molecule, antibody, peptide, peptidomimetic or has an effect on MSHS substrate. However, Tartaglia teaches methods for identifying compounds that modulate gene expression and/or gene product activity (001.6 line 1-5) wherein the screened compounds include peptides, antibodies, peptidomimetics, small organic molecules, agonists and antagonists of the gene (col.29 line 27-52). Although Tartaglia does not specifically teach antisense

nucleic acids used as the test compound, the reference does teach compounds can be small molecules that affect gene expression (col.2.9line 52-61). At the time of the invention, it was well known in the art that antisense nucleic acids inhibit gene expression (see "Antisense Nuclei Acid for Therapeutic and Other Applications, 1998, p.1). At the time of the claimed invention, one of ordinary skill in the art would have been motivated use the claimed compounds in the methods of Fishel because they were routinely used in the art in such methods as evidenced by Tartaglia. Moreover, at the time of the invention, one of ordinary skill in the art would have been motivated to use the aforementioned compounds in the methods of Fishel with a reasonable expectation for successfully identifying if the compound modulates MSH5 activity.

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references renders the claimed invention obvious to the ordinarily skilled artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

As indicated above, the pending claims are directed to methods for identifying candidate compounds useful as contraceptives or useful for modulating meiosis.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to arrive at Applicants' invention. Specifically, Fishel *et al.* fail to teach or suggest any association between MutS homologs, such as MSH5, and contraception or meiosis. Neither do Fishel *et al.* teach or suggest methods for identifying candidate compounds useful as contraceptives or useful for modulating meiosis. Thus, the primary reference of Fishel *et al.* relied upon by the Examiner, fails to teach or suggest the claimed invention.

Furthermore, the secondary reference of Tartaglia *et al.* relied on by the Examiner fails to make up for the above stated deficiencies in the primary reference of Fishel *et al.* Specifically, Tartaglia *et al.* disclose the discovery, identification and characterization of nucleotides that encode the Ob receptor (ObR), a novel receptor protein that participates in the control of mammalian body weight, and methods of using this Ob receptor (see, for example column 4, lines 48-58). Nowhere do Tartaglia *et al.* teach or suggest anything about MSH5 or the association of MSH5 with contraception and/or meiosis. Neither do Tartaglia *et al.* teach or suggest methods for identifying candidate compounds useful as contraceptives or useful for modulating meiosis. Thus, Tartaglia *et al.* also fail to teach or suggest Applicants' invention.

In summary, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention. For the foregoing reasons, rejection of the claimed invention is believed to be improper and Applicants respectfully request that it be withdrawn.

Rejection of Claims 13-14 and 23-29 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 13-14 and 23-29 under 35 U.S.C. §103(a) as being unpatentable over Tartaglia *et al.* (U.S. Patent No. 5,972,621). In particular, the Examiner is of the opinion that

Applicant claims a method for identifying a compound which modulates MSH5 activity, the method comprising a) contacting MSH5 with a test compound, and b) determining the effect of the test compound on the activity of MSH5. Specifically, the compound inhibits MSH5 activity, is capable of modulating MSH5 expression, is an antisense MSH5 nucleic acid, small molecule, MSH5 antibody, peptide, peptidomimetic, or has an effect on an MSH5 substrate. Tartaglia *et al.* teaches methods for identifying compounds that modulate gene expression and/or gene product activity (co1.6 line 1-5). Specifically, the methods identify compounds that interact with a gene or proteins that interact a gene (or a substrate), compounds that modulate the gene activity and/or gene levels and/or gene expression (col.29 line 10-25) and compounds that disrupt (or inhibit) normal gene interactions (col.31 line 40-50). The compounds to be screened include peptides, antibodies, peptidomimetics, small organic molecules, agonists and antagonists of the gene (col.29 line 27-52). The method comprises preparing a reaction mixture of the gene and test compound (or contacting the gene and test compound) followed by detecting gene/test compound complexes (which determines an effect on the gene) (col.31line 49 -col.32). Tartaglia does not teach the methods wherein the gene is MSH5. However, at the time of the invention, it would have been obvious to one of ordinary skill in the art to use any gene in the methods Tartaglia because they were well known processes in the art as evidenced by Tartaglia. Moreover, at the time of the invention one of ordinary skill in the art would have been motivated to practice the methods of Tartaglia with MSH5 with a reasonable expectation for successfully identifying compounds that modulate MSH5 activity. Although Tartaglia does not specifically teach antisense nucleic acids used as the test compound, the reference does teach compounds can be small molecules that affect gene expression (col.29 line 52-61). At the time of the invention, it was well known in the art that antisense nucleic acids inhibit gene expression (see "Antisense Nuclei Acid for Therapeutic and Other Applications, 1998, p.l). Therefore, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to test an antisense nucleic acid of the target gene in the methods of Tartaglia with a reasonable expectation for successfully identifying if the compound modulates the target gene's activity.

Applicants disagree that the claimed invention would have been obvious to the ordinarily skilled artisan at the time it was made for the reasons set forth above, the substance of which is re-iterated here. Tartaglia *et al.* disclose the discovery, identification and characterization of nucleotides that encode the Ob receptor (ObR), a novel receptor protein that participates in the control of mammalian body weight, and methods of using this Ob receptor (see, for example column 4, lines 48-58). Nowhere do Tartaglia *et al.* teach or suggest anything about MSH5 or

the association of MSH5 with contraception and/or meiosis. Neither do Tartaglia *et al.* teach or suggest methods for identifying candidate compounds useful as contraceptives or useful for modulating meiosis. Accordingly, Applicants respectfully submit that an ordinarily skilled artisan reading Tartaglia *et al.* would not have been motivated nor would have reasonably expected to arrive at Applicants' invention.

For the foregoing reasons, rejection of the claimed invention is believed to be improper and Applicants respectfully request that it be withdrawn.

CONCLUSION

In view of the amendments set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel claim 22, without prejudice, and amend claims 13, 23 and 29 as follows:

13. **(Amended)** A method for identifying a candidate compound ~~which modulates the activity of MSH5~~ useful as a contraceptive, comprising:

a) contacting MSH5 with a test compound; ~~and~~

b) determining ~~the effect of the test compound on~~ the activity of MSH5 in the presence and absence of said test compound; ~~to, thereby, identify a compound which modulates MSH5 activity.~~

c) selecting a compound that modulates the activity of MSH5; and

d) identifying said compound as being a candidate compound useful as a contraceptive.

23. **(Amended)** The method of claim 13, wherein said compound ~~is capable of modulating~~ modulates MSH5 expression.

29. **(Amended)** The method of claim 13, wherein said compound ~~has an effect on~~ modulates the activity of an MSH5 substrate.

APPENDIX A

13. A method for identifying a candidate compound useful as a contraceptive, comprising:

a) contacting MSH5 with a test compound;

b) determining the activity of MSH5 in the presence and absence of said test compound;

c) selecting a compound that modulates the activity of MSH5; and

d) identifying said compound as being a candidate compound useful as a contraceptive.

14. The method of claim 13, wherein said compound inhibits the activity of MSH5.

23. The method of claim 13, wherein said compound modulates MSH5 expression.

24. The method of claim 23, wherein said compound is an antisense MSH5 nucleic acid molecule.

25. The method of claim 13, wherein said compound is a small molecule.

26. The method of claim 13, wherein said compound is an MSH5 antibody.

27. The method of claim 13, wherein said compound is a peptide.

28. The method of claim 13, wherein said compound is a peptidomimetic.

29. The method of claim 13, wherein said compound modulates the activity of an MSH5 substrate.

30. A method for identifying a candidate compound useful as a contraceptive, comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) determining the expression of the MSH5 gene or the activity of MSH5 in the presence and absence of said test compound;

c) selecting a compound that modulates the expression of the MSH5 gene or the activity of MSH5; and

d) identifying said compound as being a candidate compound useful as a contraceptive.

31. A method for identifying a candidate compound useful for modulating meiosis in a cell, comprising:

a) contacting MSH5 with a test compound;

b) determining the activity of MSH5 in the presence and absence of said test compound;

c) selecting a compound that modulates the activity of MSH5; and

d) identifying said compound as being a candidate compound useful for modulating meiosis in a cell.

32. A method for identifying a candidate compound useful for modulating meiosis in a cell, comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) determining the expression of the MSH5 gene or the activity of MSH5 in the presence and absence of said test compound;

c) selecting a compound that modulates the expression of the MSH5 gene or the activity of MSH5; and

d) identifying said compound as being a candidate compound useful for modulating meiosis in a cell.

BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
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Expires: August 5, 2003

Harry I. Moatz
Director of Enrollment and Discipline